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Aspirin is associated with lower melanoma risk among postmenopausal Caucasian women: the Women's Health Initiative

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Abstract

Background—Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with decreased risk of gastric, colorectal, and breast cancer. However, the impact of NSAIDs on risk of melanoma has been inconsistent. We evaluated the association between NSAID use and cutaneous melanoma risk in the WHI Observational Study (WHI OS).

Methods—At study entry, use of aspirin (ASA) and non-aspirin NSAIDs was assessed among 59,806 postmenopausal Caucasian women aged 50 to 79. We used Cox proportional hazards models after adjusting for participant skin type, sun exposure history, and medical indications for NSAID use among other confounders.

Results—During a median follow-up of 12 years, 548 incident melanomas were confirmed by medical review. Women who used ASA had a 21% lower risk of melanoma (HR: 0.79, 95% CI: 0.63-0.98) relative to non-users. Increased duration of ASA use (<1 year, 1-4 years, and ≥5 years) was associated with an 11% lower risk of melanoma for each categorical increase (p_{trend}=0.01), and women with ≥5 years use had a 30% lower melanoma risk (HR 0.70, 95% CI: 0.55-0.94). In contrast, use of non-ASA NSAIDs and acetaminophen were not associated with melanoma risk.

Conclusions—Postmenopausal women who used ASA had a significantly lower risk of melanoma, with longer duration of ASA use associated with greater protection. Although this study is limited by the observational design and self-report of NSAID use, these findings suggest that ASA may have a chemopreventive effect against the development of melanoma and warrant further clinical investigation.

Keywords

Aspirin; anti-inflammatory agents, non-steroidal; melanoma; female; incidence

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INTRODUCTION

Melanoma incidence has been rising steadily[1], which has prompted investigation of primary prevention strategies[2]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin (also referred to as acetylsalicylic acid, or ASA) and non-aspirin NSAIDs, has been associated with a decreased risk of a variety of cancers, including gastric[3], colorectal[4], and breast cancer[5]. Thus, interest in NSAIDs' chemopreventive benefits for other malignancies, such as melanoma, has grown.

NSAIDs, which inhibit cyclooxygenase (COX) enzymes, may prevent carcinogenesis through both COX-dependent and COX-independent mechanisms[6]. COX-1 is constitutively expressed in human tissue, while COX-2 is an indicator of inflammation and has been implicated in the development of cancer[7]. Human melanoma cell lines over-express COX-2[8], and high COX-2 levels are associated with melanoma progression[9]. Thus, COX-2 inhibition by NSAIDs may reduce melanoma development and progression. In addition, NSAIDs inhibit activation of nuclear factor-kappaB (NFkB), a transcription factor that promotes inflammation and reduces apoptosis, through a COX-independent mechanism[10].

Evidence from observational studies investigating the association between NSAID use and risk of melanoma has been inconsistent. Some case-control studies[11-13] have found a significant association between intake of NSAIDs and lower melanoma risk. In contrast, a randomized trial of alternate-day low-dose ASA[14] and two large cohort studies[15, 16] failed to show a significant association between NSAID use and melanoma.

Using the Women's Health Initiative (WHI) Observational Study (OS), designed to evaluate new risk indicators and biomarkers for disease in postmenopausal women[17], we investigated whether NSAIDs are associated with lower risk of cutaneous melanoma. As light skin pigmentation is the major risk factor for melanoma and approximately 95% of cutaneous melanoma cases occur in Caucasians[18], we focused on this population in the WHI.

METHODS

Study Design

The design of the WHI OS (NCT00000611) has been described previously, as have the eligibility criteria and recruitment methods[17, 19]. In brief, the OS enrolled 93,676 postmenopausal women aged 50 to 79 years between 1993 and 1998 at 40 Clinical Centers throughout the U.S. Most participants in the cohort were initially screened for the randomized trials and found to be ineligible or unwilling to participate, but were still interested in and eligible for participating in the OS. Enrollment in the OS required women to have a minimum predicted survival of 3 years[19].

Consistent with the typical predominance of melanoma cases among Caucasians, only seven non-Caucasian women developed melanoma during follow-up in the WHI OS. Thus, we limited our cohort to OS women of Caucasian race/ethnicity (N=78,413) and further excluded participants missing covariates included in the fully adjusted scientific model, yielding a final cohort of N=59,806. Participants were followed for as long as possible (e.g., ≤10 years for women enrolled in the OS but not in the Extension Study, and ≤15 years for those women who additionally enrolled in the Extension Study). All procedures and protocols were approved by the Institutional Review Boards at each participating institution, and all participants provided written informed consent.

Data Collection

Demographics, medical history, diet and supplement use, physical activity, smoking status, and physical measures were obtained by questionnaire, interview or physical exam at baseline. Regional solar radiation, reported in langleys (1 langley = 1 g-cal/cm^2), was based on the amount of sunlight reaching the Clinical Center sites as measured by the US Weather Bureau[20].

Sun exposure variables were collected in a questionnaire four years after study entry. Women reported average daily time spent in the sun (<30 minutes, 30 minutes to 2 hours, ≥2 hours), during summer and the remainder of the year, in their childhood, teens, thirties, and at their current age. Skin reaction to the sun (burn/tan) after 45 to 60 minutes in first summer sun was recorded. Sunscreen use in the past year, if outdoors greater than 10 minutes, was reported along with strength (e.g., sun protection factor, SPF). The possibility of recall bias of sun exposure history in participants with melanoma was explored by comparing the distribution of self-reported exposure pre- and post-diagnosis.

Measurement of Exposure

Baseline medication intake was collected using an interview-administered questionnaire, which may be accessed at cleo.whi.org (Form 44 – Current Medications)[21]. Participants were asked: “Do you take aspirin pills or powders, for example, Anacin, Bufferin? Do you take ibuprofen tablets or capsules, for example, Advil, Motrin, or Nuprin?” If participants reported a minimum of twice weekly use for the prior 2 weeks, the drug type, strength, and duration of use were recorded. Medication data were validated by checking prescription records and bottle labels[5]. Medication use was recorded again at year 3 when participants returned for a second clinical visit.

To minimize multiple comparisons, three mutually exclusive exposure groups were defined to allow for a single, three-way comparison. Participants were divided into those that reported no NSAID use at baseline (N=35,529) versus those who used NSAIDs. Among the women who used NSAIDs, those that reported ASA use were defined as ASA users (N=15,089) and included women who reported concurrent use of non-ASA NSAIDs (n=2,857). Finally, non-ASA NSAID users were defined as participants that reported only non-ASA NSAID use (N=9,188).

Outcome of Interest

Our primary outcome of interest was time from study entry to development of melanoma, where participants were censored at death or at their last date of follow-up. Participants reported medical outcomes, including melanoma, in an annual questionnaire. Cutaneous melanoma cases were confirmed by adjudication of pathology and medical records, and coded following the ICD-O-2 coding scheme.

Statistical Analysis

Cox proportional hazards techniques were used to address: 1) whether the risk of melanoma differs among the three exposure groups (ASA users, non-ASA NSAID users, and NSAID non-users), and 2) whether the duration of NSAID use affects melanoma risk. The first model compared the hazard ratio of melanoma among the three user groups. The second model investigated duration of NSAID use (<1 year, 1-4 years, ≥5 years) as an ordered, categorical variable. For both models, we report corresponding hazard ratios (HRs) with 95% confidence intervals (CIs) that adjust for the following potential confounders: age, education, body mass index (BMI), smoking status, vitamin D intake, physical activity, history of non-melanoma skin cancer (NMSC), history of melanoma, skin reaction to the sun, regional solar radiation, childhood and current summer sun exposure, sunscreen use,

time since last medical visit, NSAID and acetaminophen categories, and medical indication for NSAID use (including history of cardiovascular disease, arthritis, and migraine). To identify potential residual confounding by analgesic use, we also performed the above analyses for acetaminophen use, which is a non-NSAID analgesic.

To assess whether the effect of NSAID use on the hazard of melanoma varied by pre-specified baseline risk factors for skin cancer, interaction effects between the potential modifier and the user groups were assessed. Previous studies have shown that melanoma risk is associated with history of skin cancer, smoking status[22], intermittent and potentially ambient ultraviolet (UV) exposure[23, 24], and perhaps vitamin D intake[25]. Thus, eight potential pre-specified modifiers included: 1) age, 2) history of NMSC, 3) history of melanoma, 4) smoking status, 5) childhood summer sun exposure, 6) current summer sun exposure, 7) regional solar radiation, and 8) vitamin D intake.

All statistical analyses were completed using SAS 9.2 (SAS Institute Inc, Cary, NC.). All statistical tests were two-sided and conducted at the 0.05 level of significance.

RESULTS

In this cohort, 59,806 Caucasian women were deemed eligible for our study. Table 1 presents select descriptive statistics on our sample by exposure group. At baseline, 25% of the women reported use of ASA at least twice in the prior 2 weeks, 15% reported exclusive use of non-ASA NSAIDs at least twice in the prior 2 weeks, and 59% of the women reported no regular use of NSAIDs in the prior 2 weeks. Of the ASA users, 25% reported low-dose (≤81mg) ASA use. Among the non-ASA NSAID users, ibuprofen and naproxen were the most commonly used medications, and none reported use of selective COX-2 inhibitors. At the year 3 clinical visit, 59% of ASA users and 38% of non-ASA NSAID users reported continued use of the same medications.

While the three exposure groups had statistically significant differences in covariates (Table 1), these were small percentage differences and are more reflective of the large sample size of the WHI. Nonetheless, these factors were included in our multivariate models. The most important predictors of melanoma risk, prior NMSC and melanoma history, were not different among the 3 groups. Overall, women who used ASA were older than women in the other two exposure groups (Table 1). Non-ASA NSAID users had the highest proportion of obesity and NSAID non-users had the lowest. Not surprisingly, more ASA users reported a history of cardiovascular disease and more non-ASA NSAID users reported a history of arthritis. NSAID users were more likely to have had a medical visit within the past year than NSAID non-users. Of note, ASA and non-ASA NSAID users tended to reside in areas with lower regional solar radiation (langleys) than NSAID non-users, and this was adjusted for in the multivariate models.

During a median follow-up of 12 years, 548 incident melanomas developed and were physician-adjudicated. There were 289 melanoma in-situ cases, 255 invasive melanomas, and 4 cases were classified as unknown. A total of 115 cutaneous melanoma cases (0.76%) were reported among women who used ASA compared to 89 cases (0.97%) in non-ASA NSAID users and 344 (0.97%) in NSAID non-users (global p-value=0.07; Table 2). The majority of melanoma cases (94%) occurred in women without a history of melanoma.

Type of NSAID Use, Duration of Use, and Risk of Melanoma

ASA use was significantly associated with a 21% lower risk of melanoma relative to NSAID non-users (HR: 0.79, 95% CI 0.63-0.98; Table 3). While the aforementioned global p-value for overall category of use was only borderline significant, the hazard ratio for aspirin users

versus NSAID non-users indicates that there was a significant difference in melanoma risk between these two groups. There was an effect of duration of ASA use on the hazard of melanoma as well. Specifically, each incremental increase in duration of ASA use (<1 year, 1-4 years, and ≥5 years) was associated with an 11% lower risk of melanoma (p_{trend}=0.01; Table 3). Risk of melanoma was 30% lower with ASA use ≥5 years (HR: 0.70, 95% CI: 0.55-0.94). The association between ASA use and risk of melanoma did not differ by known and potential skin cancer risk factors such as age, history of NMSC, history of melanoma, smoking status, childhood summer sun exposure, current summer sun exposure, regional solar radiation, or vitamin D intake at baseline in pre-specified subgroup analyses (data not shown, all p-values for interaction >0.1).

In contrast, non-ASA NSAID use was not associated with risk of melanoma relative to NSAID non-users (HR: 1.05, 95% CI 0.83-1.34; Table 2). There was no association between duration of non-ASA NSAID use and melanoma risk ($p_{categorical}$=0.8; Table 3). In addition, there was no interaction between non-ASA NSAID use and the eight pre-specified subgroups (data not shown, all p-values for interaction >0.1).

We also determined the relationship between acetaminophen use (a non-NSAID analgesic) and melanoma risk. Acetaminophen use was not associated with risk of melanoma relative to acetaminophen non-users (HR: 0.89; 95% CI: 0.68-1.17), nor was there an association with duration of use ($p_{categorical}$=0.2).

Sensitivity Analyses

As a sensitivity analysis, we also performed a two-way comparison of NSAID use (e.g. any ASA use versus no ASA use, and any non-ASA NSAID use versus no non-ASA NSAID use). These groups were not mutually exclusive and included concurrent use of other NSAIDs. Similar to the findings from the primary analysis, ASA use was associated with lower melanoma risk (HR: 0.78, 95% CI: 0.63-0.96, p=0.02), and non-ASA NSAID use was not associated with melanoma risk (HR: 1.02, 95% CI: 0.82-1.27, p=0.9).

To evaluate potential recall bias of sun exposure history, we compared pre- and post-diagnosis reports of sun exposure in women diagnosed with melanoma. Chi-square tests of association did not suggest significant differences in reporting of past sun exposure (all p-values >0.1).

DISCUSSION

In the WHI Observational Study, aspirin use was significantly associated with a 21% lower risk of melanoma relative to NSAID non-users in postmenopausal Caucasian women followed for a median of 12 years. Increased duration of ASA use was associated with greater protection, with ASA use for ≥5 years associated with a 30% lower risk of melanoma (p_{trend}=0.01). In contrast, neither non-ASA NSAID use nor acetaminophen use were associated with melanoma risk.

The WHI OS is the first cohort to show an association between aspirin use and risk of melanoma in postmenopausal Caucasian women, and is consistent with prior case-control studies demonstrating a relationship between NSAID use and lower melanoma risk[11-13]. Similar to our findings, two large case-control studies[12, 13] found different relationships among aspirin use, non-aspirin NSAID use, and risk of melanoma. In a Dutch population-based case-control study by Joosse et al[12], using national pharmacy and pathology databases, women with continuous low-dose ASA use were half as likely to develop melanoma. No association was evident between non-aspirin NSAID use and melanoma risk. However, the authors noted that non-aspirin NSAIDs were commonly prescribed “as

needed" and there were few continuous users, which could be a limitation of the study[12]. A U.S. case-control study by Curiel-Lewandrowski et al[13] similarly demonstrated that continuous aspirin use for >5 years was associated with a 56% lower melanoma risk among women. In contrast, non-aspirin NSAID use was not associated with risk of melanoma among women, although continuous use >5 years was associated with lower melanoma risk among men and women combined[13]. As with the Dutch case-control study, the authors commented that few non-ASA NSAID users reported frequent use in comparison to aspirin users. Similar to these studies, infrequent non-ASA NSAID use in the WHI may provide an explanation for the lack of association between non-ASA NSAID use and melanoma risk in our analysis. Another potential explanation is that aspirin may have properties that other non-ASA NSAIDs lack[26]. Aspirin has been shown to downregulate anti-apoptotic genes such as BCL2, in addition to upregulating several tumor suppressor genes (e.g., ALOX15 and PAWR)[6]. Furthermore, aspirin induces reactive oxygen species and mitochondrial toxicity in melanoma cell lines, promoting cell apoptosis[27]. Aspirin may have selective protection against melanoma, specifically mediated by tyrosinase that is highly expressed in melanoma cells[27].

Our findings differ from those of a randomized clinical trial[14], the Women's Health Study (WHS), and two cohort studies[15, 16]. The WHS is a randomized 2×2 factorial trial of alternate-day low-dose aspirin (100 mg) and vitamin E in the primary prevention of cardiovascular disease and total cancer among women aged 45 years or older[14]. During an average intervention period of 10 years, there were 138 melanoma cases among nearly 40,000 women, but there was no effect of alternate-day low-dose aspirin on melanoma risk in post-hoc analyses[14]. In contrast to other randomized data[4, 28, 29], the trial also found no effect of aspirin on total cancer and colorectal cancer incidence, or total cancer mortality[14]. The authors[14] and others[6, 28] note that the alternate-day low-dose aspirin may have been inadequate for cancer chemoprevention. Of note, 75% of women in our study reported regular or extra-strength aspirin use and had a longer follow up period. In the Vitamin and Lifestyle (VITAL) cohort study, aspirin use (baby or regular strength) was not associated with melanoma risk in 63,809 men and women, although aspirin exposure was recorded from any period within the previous 10 years and use at study baseline was not required[15]. Similarly, in the Cancer Prevention Study II Nutrition Cohort (CPS-II), aspirin use was not associated with risk of melanoma, but the authors combined less than daily use, low-dose use, and past use as there was insufficient statistical power to examine each individually, and did not adjust for known skin cancer risk factors (e.g., family history, skin type, sun exposure)[16].

Our finding that increased duration of aspirin use was associated with lower risk of melanoma after extended follow-up is consistent with studies of other malignancies, particularly colorectal cancer, that reported benefit after several years of aspirin use and extended follow-up (e.g., 10 to 20 years)[4, 30]. In 2009, an expert group at the International Conference on Cancer Prevention considered an antitumor effect of aspirin and sulindac to be "very probable," and an effect of other NSAIDs to be "possible"[31]. While aspirin use is not recommended for cancer prevention in the general population, it has been recommended as part of standard of care for chemoprevention in patients with Lynch Syndrome, a form of hereditary colorectal cancer, after a trial found a significant protective effect of aspirin intervention at 10 years' follow-up but not prior[30]. The combined cardiovascular benefits and potential antitumor effects of aspirin are particularly intriguing in the context of preventive medicine, but must be weighed against well-known risks, such as gastrointestinal bleeding.

Limitations of this study include the self-report nature of medication usage. However, medication data were obtained by an interview-administered questionnaire that included

specific questions regarding NSAID use and were validated with pill-bottle labels and/or prescription records. While we adjusted for many potential confounders, including skin cancer risk factors and medical indications for NSAID use in this observational study, we lacked data on family history of melanoma, eye and hair color, and cannot completely exclude residual confounding as an explanation for these findings. Strengths of this study include detailed information on participant skin type, sun exposure and sun protection habits, and prior history of skin cancer, which are important melanoma risk factors that other studies may not have captured[12, 14, 16]. Interestingly, self-report of past sun exposure was similar among those who completed the questionnaire pre- versus post-melanoma diagnosis in year 4, supporting prior arguments that recall bias in melanoma cases may be minimal[32, 33]. Additional strengths of the study include the large cohort with wide geographic diversity (high versus low UV exposure sites), a relatively large number of melanoma cases that were physician-adjudicated, and the lengthy follow-up time. In conclusion, we found that postmenopausal Caucasian women who used aspirin had a significantly lower risk of melanoma and furthermore, that increased duration of use was associated with greater protection against melanoma. These findings suggest that aspirin may have a chemopreventive effect against the development of melanoma and warrant further clinical investigation.

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Condensed Abstract: Aspirin use is associated with lower risk of melanoma among 59,806 postmenopausal Caucasian women in a prospective cohort. Longer duration of ASA use is associated with greater protection.

Table 1

Demographic characteristics and melanoma risk factors by nonsteroidal anti-inflammatory drug (NSAID) use (Aspirin vs non-aspirin) in the WHI Observational Study

Covariate	Aspirin user	Non-aspirin NSAID user	NSAID non-user	Total	p-value
N *Percent (%)*	15,089 25.2	9,188 15.4	35,529 59.4	59,806	
Median Follow-up Time (years)	11.3	11.9	11.9	11.9	
Age, years (%)					<.0001
50-59	23.3	33.7	34.6	18,909	
60-69	46.9	45.6	44.4	27,019	
70-79	29.8	20.7	21.0	13,878	
Education, (%)					<.0001
Less than high school	19.9	20.1	18.4	11,371	
Some school after high school	37.1	38.4	35.1	21,607	
College degree or higher	43.1	41.5	46.5	26,828	
BMI, kg/m^2 (%)					<.0001
<25	41.7	34.3	46.6	26,002	
≥25-30	35.5	34.7	33.2	20,336	
≥30	22.8	31.1	20.2	13,468	
Smoking, (%)					<.0001
Never	49.3	48.2	50.8	29,905	
Past	45.4	46.6	43.7	26,658	
Current	5.4	5.3	5.5	3,243	
Total vitamin D intake[1], IU (%)					<.0001
<200	17.0	18.1	20.0	11,326	
200-<400	35.1	36.2	35.7	21,298	
400-<600	23.5	23.4	22.7	13,764	
≥600	24.4	22.3	21.6	13,418	
History of NMSC, (%)					0.07
No	90.0	90.5	90.6	54,082	
Yes	10.1	9.5	9.4	5,724	
History of melanoma, (%)					0.23
No	98.5	98.4	98.7	58,960	
Yes	1.5	1.6	1.4	846	
Last medical visit within 1 year, (%)					<.0001
No	13.1	12.3	17.5	9,334	
Yes	86.9	87.7	82.5	50,472	

Covariate	Aspirin user	Non-aspirin NSAID user	NSAID non-user	Total	p-value
Cardiovascular disease ever, (%)					<.0001
No	71.6	83.3	85.1	48,687	
Yes	28.4	16.7	14.9	11,119	
Arthritis ever, (%)					<.0001
No	48.5	29.0	59.1	30,984	
Yes	51.5	71.0	40.9	28,822	
Migraine ever, (%)					<.0001
No	86.3	85.4	89.1	52,530	
Yes	13.7	14.6	10.9	7,276	
Regional solar radiation, langleys[2] (%)					<.0001
300-325	36.4	33.7	30.2	19,299	
350	20.5	18.5	22.4	12,735	
375-380	10.6	11.8	10.9	6,549	
400-430	15.2	18.1	15.8	9,566	
475-500	17.3	17.9	20.8	11,657	
Skin reaction to the sun, (%)					<.0001
Tans, does not burn	37.2	35.1	35.1	21,313	
Burns, then tans	24.3	25.1	26.2	15,288	
Burns, then tans minimally	27.1	28.2	27.1	16,295	
Burns, does not tan	11.5	11.7	11.6	6,910	
Average daily time outdoors in summer as a child, (%)					0.04
<30 minutes	2.1	1.9	2.3	1,325	
30 minutes to 2 hours	25.9	25.1	26.1	15,471	
≥2 hours	72.0	72.9	71.6	43,010	
Average daily time outdoors in summer now, (%)					<.0001
<30 minutes	31.5	32.3	29.5	18,180	
30 minutes to 2 hours	50.2	49.9	50.3	30,049	
≥2 hours	18.3	17.8	20.2	11,577	
Sunscreen SPF, (%)					0.01
None	47.6	46.5	46.6	28,019	
SPF 2-14	4.6	5.0	5.1	2,947	
SPF 15-25	30.8	30.0	30.6	18,280	
SPF 25+	17.0	18.5	17.7	10,560	

*Percentages may not total 100% because of rounding. NSAID=nonsteroidal anti-inflammatory drug; GED =general equivalency diploma; MET=metabolic equivalent tasks; NMSC=non-melanoma skin cancer; SPF=sun protective factor

[1]From diet and supplements

[2]Based on the mean annual amount of sunlight reaching the clinic site as measured by the US Weather Bureau; 1 langley = 1 g-cal/cm^2

Table 2

Association between NSAID use and incident melanoma in the WHI Observational Study

NSAID Type[1]	Melanoma cases/Total users	Incidence per 100,000 person-years	Age-adjusted HR (95% CI)	Fully-adjusted HR (95% CI)*
NSAID non-users	344/35,529	87.1	1.00 (reference)	1.00 (reference)
ASA users	115/15,089	69.8	0.80 (0.65, 0.99)	0.79 (0.63, 0.98)
Non-ASA NSAID users	89/9,188	87.9	1.02 (0.81, 1.29)	1.05 (0.83, 1.34)

*Fully adjusted model includes age, education, BMI, smoking status, vitamin D intake, physical activity, history of NMSC, history of melanoma, skin reaction to the sun, regional solar radiation, childhood and current summer sun exposure, sunscreen use, time since last medical visit, NSAID category of use, acetaminophen use, and medical indication for NSAID use

[1]Global p-value for overall category of use was 0.07.

Table 3

Association between NSAID duration of use and incident melanoma in the WHI Observational Study

NSAID Type	Melanoma Cases	Age-adjusted HR (95%CI)	Fully-adjusted HR (95%CI)*
ASA [1]			
None	433	1.00 (reference)	1.00 (reference)
<1 year	22	0.90 (0.82, 0.98)	0.89 (0.82, 0.98)
1-4 years	51	0.81 (0.67, 0.96)	0.79 (0.67, 0.96)
≥5 years	42	0.73 (0.55, 0.94)	0.70 (0.55, 0.94)
	p linear trend	0.02	0.01
Non-ASA NSAID			
None	440	1.00 (reference)	1.00 (reference)
<1 year	26	0.87 (0.59, 1.30)	0.92 (0.62, 1.37)
1-4 years	50	1.10 (0.82, 1.47)	1.15 (0.85, 1.55)
≥5 years	32	0.97 (0.67, 1.38)	0.94 (0.66, 1.36)
	p categorical	0.8	0.8

* Fully adjusted model includes age, education, BMI, smoking status, vitamin D intake, physical activity, history of NMSC, history of melanoma, skin reaction to the sun, regional solar radiation, childhood and current summer sun exposure, sunscreen use, time since last medical visit, NSAID duration of use, acetaminophen duration of use, and medical indication for NSAID use

[1] In the model of categorical duration of use (<1 year, 1-4 years, ≥5 years), ASA use was associated with a linear decreasing risk of melanoma with each categorical increase, thus the ASA model presented is for linear trend.